Rational Use of Multiple Same Class Psychiatric Medications

The purpose of this series, *Putting Evidence Into Practice*, is to give doctors and their staff the information necessary to ensure quality and effective drug therapy. Because increased side effects are likely as additional medications are introduced, the goal of pharmacotherapy is to use the least number and amount of medications to produce maximal functional improvement with the least disturbing side effects. Two significant factors in patients' poor adherence to medications that compromise treatment effectiveness are: increased complexity in administration of multiple drug treatment regimens; and, intolerability of side effects. This monograph presents a snapshot of current best thinking regarding the simultaneous use of same class medications. We hope you will find it useful as you plan a course of drug treatment for your patients.

Concomitant use of Multiple Antidepressants

Depression that is resistant to treatment is defined as *the inadequate response to at least one antidepressant trial of adequate dose and duration*, where one or more trials with monotherapy did not sufficiently address symptoms. An adequate trial is considered to be at least 4 weeks at the maximum recommended dose tolerated (not four weeks from introduction of the drug at lower doses during titration designed to optimize tolerability). To optimize tolerability, medications are best started at low doses with slow dose increases. In the case of depression that is resistant to treatment, it may be necessary to use more than one antidepressant. When considering the use of more than one antidepressant, base selection on known combined effects of the medications, as well as on the mechanisms of action to be targeted. In general:

1. The fewest drugs needed for effective treatment is the goal, monotherapy is preferable.

2. Psychotherapy (Cognitive-Behavioral Therapy and Interpersonal Therapy) is as effective as antidepressant medication in the treatment of mild to moderate Major Depression. Combining psychotherapy with medication can enhance the efficacy of the antidepressant.

3. When encountering depression which is not responding to adequate treatment:
    a. Consider treatment adherence problems, complicated dosing regimens, and undesirable side effect profiles.
    b. Reconsider the diagnosis.
    c. Consider the role of medical and psychiatric co-morbidity, particularly in elders, including the possibility of other medications that may inhibit antidepressant effectiveness, substance abuse, chronic pain, personality disorders, psychosocial stress, anxiety disorders, or a seasonal affective disorder component.
    d. Consider the use of ECT as an alternative to additional anti-depressants that may be ineffective or risk morbidity.

4. When trials of single antidepressants have been ineffective, augmentation strategies may be employed.

5. Before terminating a medication due to a perceived lack of response, ensure that the medication in question is given an adequate trial period in which to work and ensure that the medication in question has been taken at the recommended, therapeutic dosage level, consistently.

6. When switching antidepressants, monitor patient blood levels:

    a. If using an SSRI, consider first switching to another SSRI.
    b. Switch from SSRI to mixed action reuptake inhibitor (e.g., venlafaxine [Effexor]).
    c. Switch from SSRI to bupropion (Wellbutrin).
    d. Switch from SSRI to mixed action antidepressant (e.g., mirtazapine (Remeron), nefazodone [Serzone], tricyclic antidepressant).

    Additionally, while tapering one antidepressant and beginning another, there is the risk of assuming that the *combination* of medications and not the *new* medication resulted in improvement. In fact, such a conclusion is not possible to make without first tapering the initial medication. After a cross titration/taper of the medicines, the tapered medicine must be completely discontinued **before drawing conclusions about the efficacy of the new medicine.**

7. There is substantial evidence to suggest that MAO inhibitors, cognitive therapy, ECT or bright light therapy are efficacious.

8. There is some evidence to support the concomitant use of multiple antidepressants in the case of treatment-resistant depression. If the above-described modalities have been unsuccessful, first consider carefully morbidity risks for your individual patient, before attempting any combinations. Combinations should be considered based on the mechanisms of action and discrete clinical knowledge of your patient (Trivedi, 2001):

    a. Tricyclic antidepressant + SSRI (monitor blood level as SSRIs can inhibit the metabolism of tricyclics);
    b. Bupropion + SSRI;
    c. Nefazodone + SSRI, however there have been reports of toxicity in some patients; and
    d. Mirtazapine + SSRI.

9. There is little scientific evidence to suggest that combining SSRIs with atypical antipsychotics is helpful as an augmentation strategy in Major Depressive Disorder without psychotic features. (SSRIs combined with atypicals are used in other conditions including Schizoaffective Disorder, Bipolar Disorder, and Major Depressive Disorder with Psychotic Features).

10. With the exception of brief cross tapers, prescribing more than one of the following groups of medications simultaneously is strongly discouraged:

    a. SSRI – Prozac (fluoxetine), Luvox (fluvoxamine), Paxil (paroxetine), Zoloft (sertraline), Celexa (citolopram hydrobromide), Lexapro (escitalopram oxalate); and
    b. TCA – Imipramine, Amitriptyline, Clomipramine, Desipramine, Nortriptyline, Trimipramine, Protriptyline.

11. Never prescribe a MAO inhibitor (MAOI – Phenelzine, Tranylcypromine, Isocarboxazid, Selegiline) at the same time as another antidepressant (SSRIs) as mortality and morbidity may result. Please see FDA prescribing information for complete information.

Concomitant use of Multiple Sedative Hypnotics

Approximately 9% of people in the 20 to 30 year old age category and 33% to 50% of people over age 65 have some form of insomnia. Insomnia can be caused by medical illness, including heart disease, endocrinopathies and neurological disorders. It can also be caused by alcohol use, caffeine use, nicotine use, SSRIs, oral contraceptives, antiarrythmics, and thyroid conditions. Finally, it is estimated that one to two-thirds of persons with psychiatric illness also have chronic insomnia. Insomnia should not be treated with sedative hypnotic medication until the above have been adequately assessed.

By definition, chronic insomnia lasts more than three weeks. It is often multifaceted in origin; therefore, effective treatment frequently requires both pharmacological and nonpharmacological approaches.

If you are treating a person with insomnia, consider the following:

1. Assess the patient for possible medical insomnia and drug intake related insomnia.

2. Instruct the patient on the principles of good sleep habits, that is: avoiding television or other distracting activities while in bed, not remaining in bed while awake, avoiding napping, establishing a regular bedtime and wakeup schedule, and, discontinuing the use of alcohol, tobacco, caffeine and other REM-suppressant drugs.

3. Encourage the patient to engage in regular physical activity, such as walking or light exercise. Moderate exercise is beneficial for sleep at night when practiced on a regular basis.

4. Limit medication usage. Require that your patient use a sedative hypnotic only a limited number of times per week.

5. Limit duration of sedative hypnotic use. It is good practice to restrict sedative hypnotic use to no more than a four to six week period.

6. Prescribe no more than one sedative hypnotic at a time. Use of multiple sedative hypnotics can cause further deterioration of sleep structure and increase side effects.

Concomitant Use of Multiple Anticholinergics

Anticholinergics medications may **have multiple side effects**, including constipation, urinary retention, memory difficulty, habituation, dry mouth, blurred vision and even delirium. Since all anticholinergics share the same mechanism of action, simultaneous use of more than one anticholinergic is strongly discouraged.

If you are treating a person in need of anticholinergic medication, consider the following:

1. Anticholinergics should only be prescribed if it is not possible to lower the antipsychotic dose or change to an antipsychotic with fewer EPS symptoms.

2. Patients using anticholinergics should be reassessed at least every three months. Studies indicate not all patients require long-term anticholinergics.

3. No support exists for the combination use of anticholinergics.

Concomitant use of Anticonvulsants/Mood Stabilizers

There is evidence to suggest that the concomitant use of anticonvulsants/mood stabilizers is effective in treating Bipolar and Schizoaffective Disorders and many patients with these disorders require multiple medications. However, monotherapy is still the preferred practice. Therefore, it is suggested that drug therapy begin with a trial of **one** of the FDA approved agents: lithium, divalproate, risperidone, quetiapine, or olanzapine. During the trial period, it is important to achieve effective dosage levels. If monotherapy fails, proceed with a combination therapy.

If you are treating a patient in need of anticonvulsants/mood stabilizers, consider the following:

1. Initial trial of monotherapy with an FDA approved agent. Please see references for treatment guidelines.

2. In treating mania and mixed states, strongly consider discontinuing antidepressant therapy prior to adding a second anticonvulsant/mood stabilizer. Antidepressants cause increased mood instability and mania in many persons with Bipolar Disorder. Alternative treatments for Bipolar Depression include lithium and lamotrigine (Lamictal) and olanzapine and fluoxetine (Symbyax).

3. The therapeutic concentration level of valproate is between 50 and 100 μg/mL, as listed by the FDA. Consider increasing dose until limited by side effects or the 120 μg/mL serum level before considering a trial inadequate. Please Note: The 2004 PDR for Depakote varies somewhat from the FDA guideline. It states “In placebo controlled trials, patients were dosed to a clinical response with a plasma concentration between 50 and 125”.

4. The therapeutic dosage level of lithium is 0.6 to 1.2 mEq/L, as listed by the FDA. Consider increasing the lithium level up to 1.2 mEq/L unless limited by side effects. Please Note: The 2004 PDR for Eskalith varies somewhat from the FDA guidelines. It lists the acute treatment level as 1.0 to 1.5 and maintenance treatment as 0.6 to 1.2.

5. For patients with Bipolar or Schizoaffective Disorder, who are experiencing a depressive episode, after maximizing the current drug regimen, consider closely monitoring the depression and adding evidenced – based psychotherapy. Psychosocial supports may also be helpful.

6. When compared to newer antidepressants, tricyclic Antidepressants are more likely to result in increased mood labiality or mania in persons with Bipolar or Schizoaffective Disorder.

7. Bipolar Disorder is a chronic relapsing illness and it is general practice to continue mood stabilizers as prophylaxis once the patient has achieved stability. Little is known about the benefit of combining anticonvulsants/mood stabilizers over extended periods of time. Once a patient is stabilized, consider simplifying the medication regimen by tapering the adjunctive medication. Medication should not be discontinued until the patient has been in full remission for three to six months.

8. Patients and their significant others should be educated concerning signs and symptoms of recurrence, the use of recovery skills, and the availability of peer and other supports in their area. The Depression and Bipolar Support Alliance can be contacted at (800) 826-3632. The National Alliance of the Mentally Ill can be contacted at (800) 464-5767. If mood instability recurs, treatment with the medication previously effective should be initiated promptly.

References

If you would like to read more about the concomitant use of medication, consider these references:

Bipolar Algorithm and Guideline. (2002). In *Texas Medication Algorithm Project*. Retrieved November 18, 2003, from http://www.mhmr.state.tx.us/centraloffice/medicaldirector/TMAPtoc.html

Danileviciute, V., & Sveikata, A. (2002). Contemporary approach to pharmacological and clinical aspects of novel antidepressants. *Medicina, 38*, e231-e239.

Fava, M. (2003). Diagnosis and definition of treatment-resistant depression. *Biological Psychiatry, 53*, 649-659.

Lam, R. W., Wan, D. D., Cohen, N. L., & Kennedy, S. H. (2002). Combining antidepressants for treatment resistant depression: A review. *J Clinical Psychiatry, 63*, 685-693.

Perry, P. J., Alexander, B., & Liskow, B. L. (1997). *Psychotropic Drug Handbook* (7 ed.). American Psychiatric Publishing, Inc.

Sachs, G. S., Printz, D. J., Kahn, D. A., Carpenter, D., & Docherty, J. P. (2000, April). Medication treatment of bipolar disorder 2000. In *Expert Consensus Guideline Series*. The McGraw Hill Companies, Inc. Retrieved November 18, 2003, from http://www.psychguides.com/ecgs4.php

Shelton, R. C. (2003). The use of antidepressants in novel combinations. *J Clinical Psychiatry, 64*(Suppl. 1), 14-18.

Thase, M. (2003). New approaches to managing difficult-to-treat depression. *J Clinical Psychiatry, 64*(Suppl. 1), 3-4.

Trivedi, M. H., & Kleiber, B. A. (2001). Algorithm for the treatment of chronic depression. *J Clinical Psychiatry, 62*(Suppl. 6), 22-29.